REMARKS/ARGUMENTS

Claims 1-21, 23-25 and 29 are pending in the present application. Claims 1-21, 23-25 and 29 stand rejected under 35 U.S.C. § 103(a). No claims are allowed. This Action is not final.

Applicants appreciatively acknowledge the Examiner's effort in the thorough and comprehensive Official Action that is the subject of this Response. That being said, it is respectfully submitted that the Examiner's conclusion of obviousness is in error and actually goes against the teachings of the art of record. Applicants previously amended the pending claims to emphasize the patentably distinct features of the present invention which distinguish it over the art. It is respectfully submitted that this Response addresses all of the issues raised by the Examiner in the above-identified Office Action and that the subject application now is in condition for allowance. Accordingly, reconsideration of the subject application is requested in view of the following discussion.

Claim Rejections Under 35 U.S.C. § 103

The Examiner has rejected claims 1-21, 23-25 and 29 under 35 U.S.C. § 103(a) as being unpatentable over Clark et al. (US Patent No 5,641,510) and further in view of Rose et al. ("Evaluation of Sodium Colistimethate Aerosol") and Catchpole et al. ("A reassessment of in-vitro activity of colistin sulphomethate sodium"). It is the Examiner's position that it would have been obvious to combine the methods for manufacturing reduced particle adhesion interior surface in capsules for storing pharmaceutical powders for aerosol delivery as taught by Clark et al. with the aerosolized colistin derivative solution and colistin solution efficacy disclosures of Rose et al. and Catchpole et al. to lead one skilled in the art to substitute colistin (or its derivatives) for the protein or antibiotic powders of Clark et al. to produce the present invention because of the expectation of producing a successful antibiotic for use in treating infections of the respiratory tract.

Applicants respectfully traverse this rejection. None of the references cited, either alone or in combination, discloses or suggests the present invention. Combining the cited references will not produce the present invention. And, in fact, without the benefit of the hindsight teachings of the present invention, the references provided by the Examiner actually teach away from the present invention.

More specifically, the Examiner's conclusion of obviousness ignores the reality that since the early 1960s and well prior to the present invention, colistin sulphomethate sodium has been available for the treatment of infections caused by Gram-negative organisms that are resistant to more common antibiotics as a solution and not as a dry powder. It has long been known in the art that colistin sulphomethate sodium, though effective against Gram-negative organisms, particularly in the form of a solution for parenteral injection or as a solution for inhaled therapy, has side effects that limit its use. For example, Catchpole et al. specifically disclose that the use of colistin sulphomethate sodium for parenteral therapy has been limited due to concerns about toxicity, but has been used as inhaled therapy for treatment of infection and in preparations for topical and ophthalmic use. More importantly, Catchpole et al. also discloses that colistin exerts its bactericidal effects by acting as a cationic detergent which causes the disruption of the bacterial cell membrane resulting in cell leakage and ultimately in cell death. Thus, colistin is functionally effective when dissolved in solution, where it can function to disrupt cell walls, and not as a dry powder.

Further, the Dodd et al. reference ("Effect of tonicity of nebulized colistin on chest tightness and pulmonary function in adults with cystic fibrosis") provided by the Examiner specifically discloses that inhalation of hypertonic nebulized colistin solution causes chest tightness and reduction in pulmonary function and is a reason for discontinuing treatment, Thus, Dodd et al. emphasize the difficulty of treating patients with overly strong solutions of colistin due to known patient tolerance issues. Accordingly, prior to the present invention, as disclosed and suggested by these references of record, colistin and its derivatives were known to function effectively as rapidly acting cationic detergent bactericides when in solution; but, when inhaled as an

aerosolized liquid this utility was significantly limited to those solutions having patient tolerable concentrations.

Moreover, it was surprisingly found by the present inventors that the micronized colistin sulphomethate sodium powders of the present invention do not clump or stick together as one would expect with colistin and colistin sulphate (see page 7 paragraph 32). Prior to the present invention, it was known in the art that in powders having a larger particle size the particles can stick together because of static forces. In contrast, it was surprisingly found by the present inventors that colistin sulphomethate sodium does not clump. Further, the absorption of water by the micronized powders of the present invention is comparatively low, ranging from approximately 5-7% by weight under normal atmospheric conditions, further reducing clumping. Thus, utilizing the teachings of the prior art, one skilled in the art would expect that colistin powders would not function well as inhaled dry powders due to powder clumping and the resultant inconsistent delivery problems and associated localized hypertonicity problems that would prevent the ongoing effective administration of the powder form of colistin to a patient's lungs. The present inventors unexpectedly showed that these teachings do not apply to the present invention.

Thus, absent the teachings of the present invention, one skilled in the art would expect that the direct inhalation of dry particles of colistin or colistin derivatives would be ineffective as the particles first must dissolve within the respiratory tract to become effective as a cell-lysing cationic detergent; and, secondly, doing so would inherently produce localized hypertonic solutions causing chest tightness and reduced pulmonary function requiring the cessation of such treatment. Simply put, prior to the present invention, the state of the relevant art taught that it was unwise to utilize dry particles of colistin or colistin derivatives in the respiratory tract or to substitute aerosolized dry particles of colistin or colistin derivatives for particles or nebulized solutions of more conventional antibiotics because doing so would produce complications requiring the cessation of treatment.

These problems are not overcome by the combination of references proposed by the Examiner. Consistent with the teachings of the prior art, Rose et al. starts with a lyophilized form of colistin derivative, sodium colistimethate, but dissolves the drug into a sterile saline solution which in turn is nebulized to form an aerosol for inhalation. Similarly, Catchpole et al. compared the in vitro activity of various concentrations of colistin solutions against clinical isolates of Gram-negative bacteria relative to the activity of more commonly used antibiotics. Clark et al. is directed to reducing the problem of dry particle adhesion and increasing the delivery dosage from capsules by washing or dusting the interior surfaces of the capsules and is particularly relevant to use with new low dosage therapeutic proteins such as recombinant human deoxyribonuclease where up to half the intended dosage can adhere to the capsule walls (see column 2 lines 28-39). Antibiotics are mentioned by Clark et al. only once in passing after listing an entire column of literally hundreds of pharmaceutical polypeptides, fragments thereof, and other pharmaceutical compounds (see column 5, line 14 through column 6, line 11). In contrast, these problems are unexpectedly and successfully addressed by the present invention which provides compositions, dosages, capsules, and methods utilizing dry micronized colistin sulphomethate sodium powders.

Without the teachings of the present invention, none of the references relied upon by the Examiner, either alone or in combination, discloses or suggests the present invention. Combining the references as suggested by the Examiner does not produce the present invention. Accordingly, the present invention is not obvious in view of the cited references and the rejection of Claims 1-21, 23-25 and 29 should be withdrawn. Claims 1-21, 23-25 and 29 are allowable over the cited references.

Applicants have presented arguments demonstrating the patentable novelty and non-obviousness of the present invention claims over the cited references. Therefore, Applicants respectfully assert that the claims contain allowable subject matter and request that their rejection be withdrawn and that the Examiner allows the presently pending claims. If the Examiner believes that a telephonic interview with Applicants or

the Applicants' attorney will advance the allowance of this case, the Examiner is requested to contact the undersigned at the telephone number provided below.

Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 50-1329.

Respectfully submitted,

Dated: 1/30/04

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